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(54) Title: PROCESS FOR THE PURIFICATION OF GABAPENTIN

(57) Abstract: A process for the preparation of gabapentin which comprises the passage of a gabapentin inorganic salt through a strong cationic ionic exchange resin, the elution of gabapentin fixed on the column, the concentration of the resultant solution and the cristallization from organic solvent, characterized in that the elution of gabapentin fixed on the column is carried out by using an ammonia and alkaline hydroxide aqueous solution, is described.

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"PROCESS FOR THE PURIFICATION OF GABAPENTIN"

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The present invention relates to a process for the preparation of gabapentin.

Gabapentin (The Merck Index XII Ed., page 733, No. 4343) is a known drug endowed with anti-epilectic activity described for the first time by Warner Lambert Co. in the US patent 4,024,175.

In the literature several processes for the preparation of gabapentin are reported (see for example the US patents 4,024,175, 5,068,413 and 5,091,567).

Substantially, all these methods foresee a final step of purification by column chromatography of an aqueous solution of a gabapentin salt, generally hydrochloride, through a weak basic ionic exchange resin.

In the patent application PCT No. WO 02/34709 in the name of the same Applicant, a process of purification that foresees the chromatography of an aqueous solution of gabapentin hydrochloride through strong cationic ionic exchange resins is described.

The process described in the above cited PCT patent application is very efficient and it allows to obtain, after concentration of the eluate and crystallization, a high pure product, almost completely free from the corresponding lactam which is a substance endowed with a certain toxicity (Von A. Enders et al., Arzneimittel Forschung, 10, (1960), 243-250).

During the chromatographic phase on cationic resin, gabapentin is fixed to the resin allowing the other substances to percolate, in particular organic impurities coming from the synthetic process.

Gabapentin is then eluted with an ammonia aqueous solution with a concentration around 3-4% and then with water.

The fractions containing gabapentin are collected and concentrated under vacuum till obtaining a solid residue from which gabapentin is isolated by crystallization from organic solvents, preferably alcoholic solvents.

The above described process itself appears [to be] optimum with regard to the purification of gabapentin.

Nevertheless, said process needs a high amount of ammonia solution (about 4500 liters at 3% for 350 Kg of gabapentin). The ammonia solution must then be drained by a biological

draining system and this results both in an increase in costs and in a prolonged utilization of the draining system itself.

We have now found a variation to the process described in the patent application PCT No. WO 02/34709 which allows to considerably reduce the amount of the used ammonia solution obtaining at the same time an equally pure product and with substantially the same yields.

Said variation consists in eluting gabapentin fixed on the strong cationic resin with an ammonia and alkaline hydroxyde aqueous solution.

Therefore, object of the present invention is a process for the preparation of gabapentin which comprises the passage of a gabapentin inorganic salt through a strong cationic ionic exchange resin, the elution of gabapentin fixed on the column, the concentration of the resultant solution and the crystallization from organic solvent, characterized by the fact that the elution of gabapentin fixed on the column is carried out by using an ammonia and alkaline hydroxide aqueous solution.

Preferably, for economic reasons purely, the alkaline hydroxide is sodium hydroxide.

Not limitative examples of strong cationic resins useful in the process of the invention are IRA120, DIAION SK1B and IMAC HP1110.

The amount of alkaline hydroxide must not exceed the molar amount of cationic resin used in order to minimize the amount of alkaline hydroxide which elutes with gabapentin forming an alkaline salt of gabapentin.

Preferably, the concentration of NH_3 in the elution solutions is around 3-4% by weight and the concentration of NaOH around 7% by weight. The ratio between NH_3 and NaOH is preferably from 1:1 to 1:2.

At the end of elution the column is washed with demineralised water.

Practically, the method object of the invention allows to substitute a relevant amount (about 60-70%) of ammonia with sodium hydroxide and this results in a significant reduction of draining time and costs of the ammonia solution.

As further collateral advantage, the eluate volume is reduced of about 20% with further reduction of costs and time.

Thus, for example, if 4500 l of an aqueous solution of NH_3 at 3% every 350 Kg of

gabapentin by the method described in the patent application PCT No. WO 02/34709 were necessary, 4100 l of an aqueous solution of NH_3 at 3% (1400 l) and a solution of NaOH at 7% (2700 l) for the same amount of gabapentin by the method object of the present invention are sufficient.

The eluate also contains a small amount of alkaline hydroxide in the form of gabapentin salt, for example sodium salt, which may possess a destabilizing effect on gabapentin.

Nevertheless, the elimination of the sodium salt can be realized by adding a small amount of mineral acid to the solution, preferably HCl.

HCl (a diluted aqueous solution) can be directly added in the eluate or after having concentrated it at about 50% by distillation i.e after having substantially removed the ammonia.

The subsequent crystallization according to known techniques removes a great part of the chlorides added, giving gabapentin containing chlorides between 30 and 70 ppm i.e. in line with pharmacopoeia requirements (less than 100 ppm).

In a practical embodiment the process of the invention comprises fixing gabapentin on a strong cationic resin, washing with water in order to remove the inorganic acid, eluting the resin with an ammonia and sodium hydroxide aqueous solution and washing the resin with demineralised water, collecting the fractions containing gabapentin, concentrating the solution till about 50%, neutralizing the present sodium salt of gabapentin with HCl, further concentrating till obtaining a thick residue, crystallizing gabapentin from alcoholic solvents.

For better illustrating the present invention the following examples are now given.

Example 1

In a glass column (diameter 45 mm, height 450 mm) endowed with porous septum, 500 ml of suitably activated and regenerated resin Diaion SK1B were charged.

A solution of gabapentin hydrochloride (652 g of solution at 14.48% equal to 94.4 g of gabapentin) was eluted through the column.

The column was then washed eluting with demineralised water about 1500 g till pH 7.

Then, a mixture (720 g) of an ammonia solution at 3% (240 g) and a solution of NaOH at 7% (480 g) was eluted through the column.

At the end the column was eluted with demineralised water till pH 7 (about 1500 g).

The fractions of eluate containing gabapentin were collected obtaining a solution (2171 g) containing gabapentin (4.25%, 92.3 g).

To the solution, 23.4 g of HCl solution at 3.99% (equal to 0.934 g of HCl) was added.

The solution was then concentrated under vacuum at a temperature below 40°C obtaining a crude (91.2 g) containing gabapentin at 97.6%.

In a 500 ml reactor under nitrogen crude gabapentin (70 g), demineralised water (34.7 g) and methanol (43.7 g) were charged.

The suspension was heated at 50°C for 30 minutes and then isopropyl alcohol (180.5 g) was added dropwise in 30 minutes.

The mixture was kept at 50°C for further 30 minutes and then it was cooled at 25°C in 2 hours and at -5°C in a further hour, keeping this temperature for further 2 hours.

The solid was filtered and washed on the filter with isopropyl alcohol cooled at -5°C.

After drying in oven at 45°C, gabapentin (64 g) was obtained with purity higher than 99%, lactam under 0.01% and 69 ppm of chlorides (expressed as Cl^-).

Claims

1) A process for the preparation of gabapentin which comprises the passage of a gabapentin inorganic salt through a strong cationic ionic exchange resin, the elution of gabapentin fixed on the column, the concentration of the resultant solution and the cristallization from organic solvent, characterized in that the elution of gabapentin fixed on the column is carried out by using an ammonia and alkaline hydroxide aqueous solution.

2) A process according to claim 1 wherein the alkaline hydroxide is NaOH.

3) A process according to claim 1 wherein the ammonia and NaOH aqueous solution is obtained by mixing an ammonia aqueous solution at 3-4% with a sodium hydroxide aqueous solution at 7-8%.

4) A process according to claim 1 wherein the gabapentin sodium salt that is present in the eluate is neutralized with an aqueous solution of HCl.

5) A process according to claim 1 which comprises fixing gabapentin on a strong cationic resin, washing with water, eluting the resin with an ammonia and sodium hydroxide aqueous solution and washing the resin with demineralised water, collecting the fractions containing gabapentin, concentrating the solution till about 50%, neutralizing by HCl the present gabapentin sodium salt, further concentrating till a thick residue, crystallizing gabapentin from alcoholic solvents.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
C-392		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2004/006513	17/06/2004	20/06/2003
Applicant		
ZAMBON GROUP SPA		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box II).

3. [ ] **Unity of invention is lacking** (see Box III).

4. With regard to the **title**,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regards to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [X] none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/006513

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C227/40 C07C227/42 C07C229/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/34709 A (NICOLI ANDREA ; ZAMBON SPA (IT); CANNATA VINCENZO (IT); CORCELLA FRANC) 2 May 2002 (2002-05-02) the whole document	1-5
Y	DYE S R ET AL: "EQUILIBRIUM SORPTION OF AMINO ACIDS BY A CATION-EXCHANGE RESIN" INDUSTRIAL & ENGINEERING CHEMISTRY RESEARCH, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 29, no. 5, 1 May 1990 (1990-05-01), pages 849-857, XP000165650 ISSN: 0888-5885 *page 849, left-hand column, paragraph 1-right-hand column, paragraph 1, experimental section, page 850*	1-5

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 September 2004	07/12/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Lorenzo Varela, M.J.

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Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 414 263 A (GOEDECKE AG) 27 February 1991 (1991-02-27) example 2	1-5
Y	WO 00/01660 A (ARRIGHI KATIUSCIA ; PAIOCCHI MAURIZIO (IT); RUSSO LAURA (IT); VILLA MA) 13 January 2000 (2000-01-13) *the whole document; in particular, page 3, lines 8-11 and the examples*	1-5

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/006513

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